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Present Concepts in Toxemia of Pregnancy

MILTON L. McCALL

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MONTHLY CLINICAL MONOGRAPHS ON CURRENT MEDICAL PROBLEMS

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Present Concepts in Toxemia of Pregnancy

MILTON L. McCALL

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Milton L. McCall

is Professor and Chairman of the Department of Obstetrics and Gynecology, University of Pittsburgh School of Medicine, and Medical Director and Chief of Staff of the Elizabeth Steel Magee Hospital in Pittsburgh. He is a Fellow of the American Gynecological Society, the American Association of Obstetricians and Gynecologists, the American College of Obstetricians and Gynecologists, the American College of Surgeons and many other professional organizations. Dr. McCall is the author of many scientific articles in the field of obstetrics and gynecology.

TOXEMIA OF PREGNANCY still stands foremost among the unsolved problems in the field of obstetrics today. While it is true that the severest types of toxemia are less common than formerly, the fact remains that in the United States in the deep South, and in other sections of the world, it is the major cause of maternal and perinatal mortality.

It is singularly significant that in the light of our present knowledge many toxemic deaths are preventable. Browne clearly points to the same conclusion by declaring that in Britain, where this disease is the leading cause of death among childbearing women, over 50% of deaths are associated with avoidable factors. Poor co-operation on the part of the patient in accepting adequate antenatal care undoubtedly plays a significant role in preventable deaths from toxemia. On the other hand, the medical profession must provide superior prenatal management for all those who seek it. In fact, our duty is not fulfilled unless through every possible means of private and public health practice we not only encourage, but also actively attempt to develop, an awareness and an educated conscientiousness among all potential mothers, including those who heretofore have been derelict in seeking necessary care. Finally, we must guard against any attitude of complacency engendered by the fact that in some parts of the United States serious toxemia is seldom seen. Fulminating toxemia may still occur in the most carefully regulated practice, and we

must be prepared to approach it intelligently and circumvent the all-too-common tendency for frenzied overtreatment which so greatly jeopardizes the ultimate recovery of the eclamptic patient.

It is the purpose of this monograph to review the latest basic and clinical investigations in the field of pregnancy toxemia and to present a method of treatment based on medical control of basic abnormalities in function, combined with appropriate obstetric management.

Unfortunately, the term "toxemia of pregnancy" has frequently been used in a loose manner, so as to represent a heterologous group of diseases encountered during pregnancy. True toxemia of pregnancy, however, is an acute disease occurring only after the 24th week of gestation and, most often, in the latter part of the 3d trimester in previously normal pregnant or puerperal women. It is characterized by hypertension, proteinuria, edema and, in certain severe cases, convulsions and coma. This condition is called pre-eclampsia in its nonconvulsive stage and eclampsia whenever convulsions and/or coma have supervened. An acute toxemia may also be superimposed on pre-existing essential hypertension or chronic glomerulonephritis, adding to the seriousness of these conditions. The incidence of pre-eclampsia-eclampsia in the United States is approximately 5% of all viable pregnancies. There is a definite geographic distribution, however, the highest incidence occurring in the deep South, and the lowest in the North. On my service at the Charity Hospital in New Orleans, toxemia occurred in 17–18% of patients. In some clinics in the North, its incidence is only 1–2%.

ETIOLOGY

The specific cause of toxemia of pregnancy is unknown. Although hundreds of theories have been proposed through the years, not one has been proved, and almost all have been discarded. It is well known that certain groups of women are prone to develop toxemia. These are primigravidas, diabetics and women with multiple pregnancies, polyhydramnios or hydatidiform mole. It is also known that patients with pre-existing hypertensive disease or chronic glomerulonephritis not infrequently develop a superimposed acute toxemia. Despite this knowledge,

nothing but the flimsiest supposition connects any of these with the true cause of the disease.

The most popular theories at present are those of uterine ischemia, the presence of a circulating specific toxin originating in the uterus, placenta or kidney, and endocrine aberration, any or all of which may or may not be associated with nutritional deficiency or the general adaptation syndrome. The uterine ischemia theory, championed by many and proposed long ago by James Young, has found new backing from Sophian, Franklin and others. Sophian has postulated that increased intrauterine pressure, or some other change bringing about a lowered circulation in the uterus, will cause a uterorenal reflex, resulting in all of the renal symptoms of the disease and ultimately all other changes which take place in severe toxemia. Schuurmans, among others, disagrees with this theory and questions Sophian's assumption that there is really a high pressure placed on the walls of the uterus. On the other hand, Smyth says that this theory cannot be discarded before ascertaining whether pre-eclamptic patients have a phase of raised intrauterine pressure before they become pre-eclamptic, and whether these patients have more frequent Branxton-Hicks contractions than do normal patients, thus stimulating the uterorenal reflex.

F. J. Browne feels that because of the several resemblances between toxemic pregnancy and Cushing's syndrome there must be a pressor substance produced in excess, since this is true in Cushing's syndrome and 90% of these patients are hypertensive. But, says he, the blood in normal pregnancy, which contains at least as much, if not more, 17-hydroxycorticosteroids as in Cushing's syndrome, must contain an oxygen-sensitive oxydase that inactivates pressor hormones from the adrenal cortex. If this is so, this would explain why cortical hormones, which in the non-pregnant person cause hypertension and edema, are without this effect in healthy pregnant women. If, from any cause, the placenta is made ischemic and its oxygen tension lowered, the protective enzyme is made ineffective with resultant hypertension and other signs of toxemia. He also suggests that postpartum toxemia may be explained by the passing of the placenta and the loss of its inactivating effect on pressor hormones. Raab and his associates, on the other hand, feel that the syndrome of toxemia of

pregnancy is caused by an overproduction of corticoids, that these, quite possibly, have their origin in the placenta and that aldosterone may occupy a prominent place in this picture. They have shown that there is a vascular hyperreactivity in toxemia quite similar to that which has been demonstrated in desoxycorticosterone acetate-treated males. The phenomenon of toxemic hypertension is interpreted as being "caused by a corticoid-induced increase of the intracellular cationic gradient and by its potentiating effects of vascular cell contractility in response to the adrenosympathogenic pressor catechol amines, and possibly also due to as yet unidentified pressor agents." They feel that the norepinephrine hyperreactivity test (response to 0.3 micrograms per kilogram per minute intravenously for 5 minutes) may be used after the 20th week of gestation for the detection of still asymptomatic pre-toxemia, so that vigorous measures may be applied in time to prevent or mitigate toxemic complications.

McGaughey and his associates of the University of Virginia have shown that in the dog acute distention of the uterus and renal cortical ischemia are probably *not* important as an etiologic factor in toxemia. They say this in contradistinction to Sophian's belief in the uterorenal complex, because, although in the dog acute distention of the uterus produces a mean decrease of 23% in the clearance of PAH, a similar reduction occurs during vaginal manipulation, or plain skin stimulation. Salerno and associates emphasize the possibility that this disease may be brought about by a disturbance of the hypothalamic-pituitary-adrenal axis, resulting in imbalance or excess of adrenal cortical steroids. They emphasize the relationship of youth, primiparity and unwed status to a general adaptation mechanism.

In 1954, Pike and Dickins reported that there was an excess of women in blood group O who suffered from toxemia of pregnancy. Further studies by Dickins and Roberts, as well as by Pearson and Pinker, found that there was no significant difference in the distribution of ABO blood groups in toxemia as compared with nontoxemic women. Another British investigation by Platt and his associates of the possible hereditary and antigenic incompatibilities between mother and fetus turned up no positive evidence along this line.

There has been no new and significant work which adds to the stature of the theory that there is a circulating toxin responsible, or to support the belief that malnutrition plays an important part. There has been no one factor shown to play a decisive or specific role either by its absence as causing toxemia or by its presence protecting against toxemia.

In summary, it may be stated that there is a fertile field for much-needed further investigation of this hodgepodge of affairs concerning the etiology of pregnancy toxemia. It has long been my feeling that there may be *multiple etiologic factors* responsible for the development of the toxemic syndrome.

PATHOLOGIC ANATOMY

In the past, our entire knowledge of toxemia of pregnancy, aside from the clinical picture, was based on the pathologic anatomy revealed at the time of autopsy. In recent times, there has been less work done along these lines. However, the latest work of Sheehan and of others is worthy of review. The main causes of death in toxemia are: cardiac failure with pulmonary edema, gross cerebral hemorrhage and renal failure. In some patients, there is evidence that prolonged coma and all three of these main causes of death are involved. Three quarters of the deaths from eclampsia occur within the first 2 days, and almost all others are during the next week. At least a third of the patients have multiple small petechial hemorrhages in the cortex of the brain, and pia-arachnoid. Occasionally, there is a large hemorrhage in the region of the basal ganglia. These may or may not burst into the ventricle. Although Sheehan states that death due to gross cerebral hemorrhage occurs in only 10% of eclamptic demise, Krupp in his study of maternal mortality over a 10-year period in the Charity Hospital in New Orleans showed that some 47% of toxemic deaths were associated with gross cerebral hemorrhage. Sheehan emphasizes that the brain is never grossly edematous, in contradistinction to the common belief. He states that when the brain is examined in the first hour after death, it is just as firm as the brain from any noneclamptic patient examined early.

The lungs of a patient dying from eclampsia exhibit a change which is quite similar to hemorrhagic bronchopneumonia throughout the whole of both lungs, and it is difficult to determine whether the infiltration of white and red cells and protein fluid into the alveoli is only a response to a local vascular disturbance which is part of eclampsia, or indicates a terminal infection. He suspects the former. In the liver, typical periportal lesions are found in about three quarters of the patients who die of eclampsia within the first day or two, but in only about one quarter of those who die later. In about 20% of patients, this condition extends to involve almost the entire liver in a diffuse hemorrhagic process, but ordinarily liver lesions are of academic interest and cannot be considered a cause of death. Approximately one sixth of eclamptic deaths are due to renal failure on the basis of lower nephron nephrosis. Occasionally, renal cortical necrosis occurs.

The so-called characteristic change in the glomeruli, represented by some thickening of the glomerular membranes, is transient and heals completely within about a week if the patient survives the actual eclampsia. The same resolution of any tubular lesion takes place. The heart commonly has subendocardial hemorrhages on the left side of the interventricular septum in about two thirds of patients. These hemorrhages are a characteristic finding, and their occurrence in eclampsia is presumably related to the acute cerebral disturbance. It is possible that they may affect the conducting system of the heart, in some instances, and be a factor in causing death, but this is as yet uncertain.

The placenta may show a pathologic lesion, namely red infarction (intervillous thrombosis) and some degrees of toxic premature separation. At present, however, there are no known pathognomonic histologic lesions, common to all placentas of toxemic women. There is diffuse trophoblastic injury and a premature aging of the placenta, all of which may well be on the basis of vascular dysfunction.

PATHOLOGIC PHYSIOLOGY

In recent years, the studies based solely on pathologic anatomy have been superseded in significance by the more dynamic approach of clinical physiology. In severe toxemia of pregnancy,

every organ of the body is affected adversely. Some of the most prominent advances made in the investigations of this disease have been in the field of pathologic physiology.

If we look at this problem in a general way, the following are the major changes which are taking place in function during the height of the disease:

1. Vasoconstriction.
2. Fluid and electrolyte retention.
3. Anoxia.
4. Hormonal imbalance.
5. Hematologic changes.
6. Neurologic hyperexcitability.

These general changes work together to affect every organ and tissue of the body in a deleterious way, causing malfunction and giving rise to the objective and subjective symptoms of the disease. The vasoconstriction seen in toxemia is generalized and is present in all of the major organs of the body. It is due to spasm of the terminal arterioles, as well as perhaps the larger capillaries. This brings about increased peripheral resistance and gives rise to the subjective symptoms of headache and blurring of vision. It also gives rise to the extremely important objective symptom of hypertension.

Hypertension puts a greater load on the heart, which has already been called on during this type of abnormal pregnancy to increase its output approximately 50%. Furthermore, augmented vascular tension is associated with an increased incidence of gross hemorrhage into organs. This is especially true in the brain, where such complication is extremely serious and one of the three common causes of death. Severe vasoconstriction in all organs brings about ischemia and tiny areas of hemorrhage due to the fact that there is fragmentation of the smaller vessels. This, combined with local tissue anoxia, can cause a serious effect on the viscera.

The abnormal retention of water and sodium is typical of this disease. In fact, this change is one of the earliest signs of mild pre-eclampsia. Edema is the result, but the cause is not exactly known. Although there is some degree of hypoproteinemia in toxemia, this is usually not of great enough degree to bring about

edema, nor is there increased capillary permeability or increased capillary blood pressure. Today, it is felt that one of the fundamental causes for edema and water and sodium retention in toxemia is an abnormal secretion of adrenal corticoids, and perhaps of sex steroids. It is also felt that the disturbances in kidney function may play a part in edema.

Anoxia is a prominent pathophysiologic change in pregnancy toxemia, and aside from that brought about in tiny areas of the viscera due to severe vasospasm and ischemia, anoxia is mainly seen during eclampsia itself. There are actually two types of anoxia that are known to exist in this syndrome. One occurs in the coma between convulsions and is present even though there is normal oxygen saturation of hemoglobin. It is here that the cells themselves are unable to take oxygen out of the blood stream or utilize it normally, and therefore this type of anoxia at least resembles histotoxic anoxia. The other type of anoxia is anoxic anoxia, which is brought about by the respiratory difficulty and depression associated with convulsion. This is associated with lowered oxygen saturation of hemoglobin, and my studies have shown that arterial oxygen saturation may be depressed as low as 39% immediately after a convulsion.

The study of the hormonal imbalance in pregnancy toxemia has produced some of the most exciting results in modern toxemia research. It has been known for a good many years that in many cases there is an increase in chorionic gonadotropins associated with a decrease of progesterone and estrogens. The excretion of corticoid hormone is considerably increased during pregnancy and even to a greater degree during pre-eclampsia. The mineralocorticoid, aldosterone, is the most potent sodium retainer yet isolated and it has been felt by some that an excess of this hormone might be the fundamental cause of toxemia. This has not been borne out, however, as further investigations have taken place.

Barnes and Quilligan, as well as Kumar and his associates, have shown that in normal pregnancy aldosterone excretion is usually high. In pre-eclampsia, on the other hand, aldosterone excretion decreases. The latter investigations have seemed to show that there is a tendency for intracellular sodium rise in toxemia, whereas in normal pregnancy the intracellular sodium concentration is

lowered. Barnes and Quilligan feel that aldosterone has not been demonstrated to be the cause of edema in toxemia, and may well be the sequel rather than the cause of the syndrome. Martin and Mills suggest that increased aldosterone secretion in normal pregnancy may be to counteract the sodium excretion effect of progesterone, and they postulate that toxemia of pregnancy is probably due to disturbance of the balance between all the sodium-retaining substances and all the sodium-excreting substances. In other words, there is more than one cause for toxemia.

Garst and Assali present a most interesting study of adrenal cortical capacity and cortisol utilization in normal and toxemic pregnancy. They found that the level of plasma 17-hydroxycorticosteroids in late pregnancy can be further elevated by the action of exogenous ACTH. The reserve capacity of the adrenal cortex is somewhat reduced in toxemia of pregnancy, whereas normally pregnant and nonpregnant subjects have similar reserve capacities. Utilization of cortisol in both normal and toxemic pregnancies did not appear to be faulty, and therefore does not seem to be a factor in the elevated levels of plasma 17-hydroxycorticosteroids found in pregnancy.

McCreary has presented further evidence recently that there is a definite increase in plasma antidiuretic activity in toxemia of pregnancy, and that this effect is related to the clinical severity of the disease. It has long been held that there is an antidiuretic hormone affecting renal function, probably through a tubular mechanism in pregnancy toxemia.

Hematologic changes center around the development of hemoconcentration in severe toxemia, as the plasma fluid goes into extravascular tissues. While it has been established that a definite, but mild, hypoproteinemia exists in toxemic pregnant women, this is probably due not only to dietary lack, but also to urinary loss of protein. In some severe cases of pre-eclampsia, and in eclampsia, there is an increased tendency toward blood clotting, probably due to increased thromboplastin thrown out into the blood stream by the placenta. This, then, is associated with fibrin deposition and ultimately, if this continues, a hypofibrinogenemic state may occur. This is especially noted in severe instances of placental abruption.

The most common chemical change in the blood is the increased uric acid seen in severe cases and which is thought to be due to increased tubular reabsorption in the kidney. While, ordinarily, serum sodium remains about normal, this may be decreased in association with a slight increase in blood urea nitrogen in patients who have been on a low-sodium diet for quite some time, or who perhaps have an associated adrenal cortical depression. Mulé and Tatum have shown this to be true, especially in patients with pre-existing hypertensive diseases, on which has been superimposed some degree of acute toxemia. It has been known for some time that occasionally when a patient collapses into shock after having had typical toxemia of pregnancy, this may be on the basis of a very low sodium in the serum.

Finally, hyperirritability of the nervous system is typical of the severely toxemic patient. This increases, usually, as the disease worsens, and in the most severe cases ultimately reaches its acme as convulsions occur.

New applications of mathematics in the physical sciences have made possible the development of new basic methods which obstetricians and gynecologists have been quick to modify to their own purposes. Such methods have been utilized to study the brain, the kidney and cardiohemodynamics in a quantitative fashion for the first time. In toxemia, the role of the brain has always been looked on as extremely important. Some of the earliest investigators even felt that the cause of the disease lay within the cerebrum; thus, Rosenstein as early as 1864 postulated that ischemia of the brain was the cause of eclampsia. Studies of this organ by me and my associates have shown that cerebral blood flow is unaltered by normal pregnancy and by toxemia of pregnancy. It has been shown, however, that cerebral oxygen utilization is significantly depressed in the coma between convulsions and that there is extremely high cerebral vascular resistance in this disease, undoubtedly caused by vasospasm. While it is evident that there is an over-all increase in cerebral vascular tonus during eclamptic convulsions, Byrum, by direct visualization of the cerebral vessels in hypertensive animals, has found that distinct local cerebral vasospasm of severe degree is also invariably present. While no definite evidence exists that vessel spasm is the cause of eclamptic convulsion, we may conclude that the presence

of such severe vascular effect is most undesirable indeed in the toxemic patient. It may well be identified with gross cerebral hemorrhage, a complication which the brain tolerates less graciously than does almost any other organ.

Disturbances in renal function undoubtedly play a great part in this disease. The latest quantitative studies show that renal blood flow and glomerular filtration rate are increased early, and to a lesser degree, throughout most of pregnancy. In toxemia, both are depressed. Therefore, less sodium and water are filtered through. There is also a very great renal tubular effect which, to some degree at least, must be under the control of the adrenal corticoids. Renal tubular reabsorption of sodium and water is increased; thus, the excretion of sodium and water by the toxemic kidney is interfered with. There is increase in peripheral vascular resistance in the kidneys due to arteriolar spasm, probably mainly in the afferent limb of the glomerulus. It is felt that ischemia and anoxia on the basis of vasoconstriction here accounts for the symptom of proteinuria in this disease.

The studies of Browne and others have shown that there is decreased blood flow in the placental area, as well as in the myometrium of the pregnant uterus in the last trimester in pregnancy toxemia. MacKay has shown that the average rate of oxygen consumption by fresh placental tissue is significantly lower in pre-eclampsia and eclampsia than in normal pregnancy of the same duration. In further work, he has also found that there is a fall in the cord oxygen levels in the fetus in cases complicated by pre-eclampsia. The order of this reduction is related to the duration of the disease, as well as to its severity. Thus, the changes described in the placenta and in the decidua, which represent pathologic anatomy in this disease would appear to be unquestionably due to the vascular effect, namely, severe vasoconstriction.

SYMPTOMATOLOGY

Not very much new work has come out in regard to the symptoms of pregnancy toxemia. However, Langmade emphasizes that epigastric pain, which is frequently a quite serious symptom and often presages convulsions, may also be due to acute esophageal, gastric or duodenal ulcer. The complications of

perforation and massive hemorrhage have been the cause of death in patients otherwise recovering from pre-eclampsia or eclampsia.

DIAGNOSIS AND DIFFERENTIAL CONSIDERATIONS

The diagnosis of toxemia of pregnancy usually can be made clinically without the performance of a large number of unusual laboratory procedures. While it is true that numerous pathophysiologic changes take place which can be detected by various laboratory tests, few of these are necessary in the diagnosis or in the clinical management of the patient. Willson and Hayashi have emphasized that those which are most helpful are relatively simple measures which can be performed in the physician's office or the hospital laboratory.

From the standpoint of scientific interest, however, there are a number of diagnostic procedures which have been re-evaluated of late and should be of interest to the student of toxemia. Uric acid levels of the blood are increased in most severely toxemic patients. Fisher believes that this test, which is quite simple, is usually diagnostic of this condition and that, furthermore, the level of uric acid is sensitive and it serves as a true mirror of the severity of the disease, and therefore is prognostic. He contends, although this has not been borne out by recent investigations of others, that high uric acid associated with normal blood urea nitrogen is a sign of toxemia of pregnancy. When both are low in a hypertensive patient, she usually has essential hypertension. When both are high, fundamental kidney disease should be suspected, and further kidney function tests should be performed. Willson and his associates repeated the Dieckmann salt test in 213 pregnant women and came to the conclusion that, on the basis of this test alone, pre-eclampsia, acute or chronic glomerulonephritis and essential hypertension with superimposed acute toxemia were indistinguishable from one another.

An interesting study of the nasal mucus smear in toxemic patients was carried out by Abou-Shabanek and his associates who showed that the absence of arborization (negative fern phenomenon) in the nasal smear is associated with pre-eclampsia or

eclampsia. They hope this may enable the physician to detect pre-eclampsia by a simple office test, as well as to guide the management and prognosis for the mother and baby during the course of the disease. It will be interesting to see whether this is confirmed by others.

It has been emphasized again and again during the past few years by a great number of authors that ophthalmoscopic examination is of great importance in the diagnosis and following of toxemic patients. Undoubtedly, this is one of the most important procedures we have in our armamentarium, and it behooves every physician who is seeing such patients to learn to use the ophthalmoscope expertly. Sadowski and his associates have pointed out the fetal prognostic value of retinal changes in toxemia. Agarwal and his co-workers have studied normal and toxemic pregnant patients from the standpoint of brachial and retinal blood pressures. They found a disproportionate rise in the retinal diastolic pressure in pre-eclampsia and eclampsia, and that retinal changes in the form of retinopathy can be correlated more accurately with the retinal diastolic pressure than with brachial blood pressures. They call this procedure ophthalmodynamometry, and recommend it as a routine technic for investigation in pregnancy.

Piper and Nofles found that recession of the near point of convergence in toxemia of pregnancy tended to parallel the degree of retinal changes. This simple test, they believe, is of great importance in the evaluation of the toxemic patient. Both Perl and Arnold, as well as Gardiner and Herdan, in very careful studies, failed to find that the flicker fusion threshold test for the prediction of the clinical syndrome of pre-eclampsia was of significance. Thus, it is now the general feeling that the early work of Brill and others has not been borne out as being of great importance in the diagnosis and prognosis of this disease.

PROGNOSIS, IMMEDIATE AND REMOTE

The risk of death for the mother in pre-eclampsia is slight, but when eclampsia with convulsions and/or coma develop, this danger is enhanced greatly. At present, in the United States, maternal mortality in convulsive eclampsia is approximately 10%.

That this need not be so high is evidenced by the fact that with the modern therapy outlined subsequently in this paper, only 1 toxemic death took place on my service at Charity Hospital in New Orleans over a period of 5½ years, whereas before this time this condition was by far the most common cause of maternal death. Maternal mortality is approximately 1% or less in pre-eclampsia. As mentioned previously, the 3 most common causes of death from eclampsia are: cardiac failure with pulmonary edema, gross cerebral hemorrhage and kidney failure. It is not unusual to see death occur after prolonged coma associated with all 3 of these complications. The incidence of fetal loss in this disease is much higher than that for the mother. This varies, according to geographic location, from 5% mortality to over 30%. Many of these deaths are on the basis of prematurity following termination of pregnancy as the last resort in the therapy of the disease.

There are unexplained fetal deaths, undoubtedly due to basic toxemic processes. In the essential hypertensive with superimposed toxemia, when early in the 3d trimester, it is not unusual for small babies to result and for mortality to be quite high on the basis of placental circulatory insufficiency. Chesley and Hellman point out that, generally speaking, the risks of maternal death, eclampsia, premature separation of the placenta and fetal death all increase with not only the severity but also the duration of the toxemia.

Gordon and Fell have recently pointed out some interesting statistics concerning the recurrence of toxemia in subsequent pregnancies. They showed that whenever a woman has had pre-eclamptic toxemia, she will develop it again in her next pregnancy in 45% of cases; if she has had it in two consecutive pregnancies, the risk of recurrence is 72%. When normal pregnancy follows a toxemic one, the risk is only 6% that toxemia will ever occur again. It is Chesley's feeling, at present, that chronic hypertensive disease seldom, if ever, is caused by true toxemia. In fact, he feels that if some such change develops, it is most likely that the diagnosis was wrong and should have been essential hypertension in pregnancy. There is no evidence at present that pure toxemia of pregnancy is ever followed by serious and chronic renal disease.

MEDICAL THERAPY OF TOXEMIA

Management of Mild Pre-Eclampsia

By mild pre-eclampsia we mean the patient who has been normal but who develops, in the latter part of pregnancy, an increase in blood pressure under 160 mm. systolic or 105 mm. diastolic, who has 2+ albuminuria or less, and maintains a good urinary output, has no cerebral or visual disturbances, no pulmonary edema, cyanosis or other symptoms of severe toxemia. All others in the absence of convulsions and coma are said to have severe pre-eclampsia.

Mild pre-eclampsia has as its precursor a state quite frequently associated with sudden excessive weight gain and the development of edema, without the usual urine or blood pressure effect. We must also remember that mild pre-eclampsia may suddenly become severe pre-eclampsia and, indeed, a mild pre-eclamptic may suddenly develop convulsions and coma in the full-blown syndrome of eclampsia itself. Therefore, we cannot be lulled into false security, even though symptoms are mild. In fact, it is the rigorous treatment of the mild pre-eclamptic and, better still, the rigorous treatment of pregnant women who show the precursory symptoms of this disease, that pays off in the long run in the prevention of toxemia.

It has been shown without question that careful and diligent prenatal care is of prime importance in prevention of toxemia of pregnancy. Unfortunately, care masquerading as adequate antenatal management is seen quite frequently, and it is in association with such a program that a high incidence of toxemia of pregnancy may be found. It is my feeling that patients should be seen at least every 3 weeks up to the 32d week, and thereafter every 2 weeks until the 36th week, and every week during the last month. Hamlin has pointed out once again the great importance of careful prenatal care. He has shown, as has been shown in numerous clinics and in private practice in the United States, that pre-eclampsia and eclampsia are much less frequent when the most careful care is administered. In his experience in Sydney, Australia, the incidence of eclampsia was 1 for every 350 clinic patients who apparently were receiving good prenatal care, until he instituted a rigid type of management. Within 2 years, the

incidence of eclampsia had been lowered to 1 in 7,000 clinic patients. At the same time, he lowered the incidence of pre-eclampsia to 1.8% from a previous incidence of 10%. He has re-emphasized the tremendous importance of evaluating the patient early, since many precursor alterations of this condition begin as early as the 12th to 16th week.

A careful review of the diet will frequently disclose that the patient has a very high carbohydrate intake; this should be adjusted so that a relatively greater amount of animal proteins is ingested. At the same time, the amount of sodium in the diet should be decreased. Instead of depending on a rise in blood pressure and the presence of albumin in the urine as the important signs of toxemia, it behooves us to keep the patient's weight gain at about ½ lb. per week, and certainly no more than ¾ lb. per week. *If a rate of gain of 8 pounds or more in any 10-week period occurs* before the 30th week, this is a dangerous and significant sign of the possible development of toxemia later. If there is slight tightening of the rings or a whitening of the infra-orbital skin, this should be looked on as representing incipient toxemia. Of course, all of this means tremendous discipline. In fact, the 3 major principles of therapy from the standpoint of good prenatal care in the prevention of toxemia are: *discipline, diet,* and *diuresis.* Bed rest is also of great importance in these patients, since diuresis will frequently take place without any further medication when this is carried out. If blood pressure rises to 140/90 or more in the presence of proved albuminuria in a catheterized urine specimen in a patient without genito-urinary infection, it is ideal to hospitalize the patient, unless she can be put to bed at home and can be depended on to be trustworthy in very close rapport with the physician.

The use of diuretics in mild pre-eclampsia is frequently important, and there has been a great deal of investigation of newer substances in recent times. In conjunction with mild sedation (for example, phenobarbital 30 mg. q.i.d.) ammonium chloride, 2 gr. q.i.d., for 4 of 7 days, or Diuril (chlorothiazide) 0.5 gr. b.i.d., and Diamox (acetazolamide) 0.25-0.5 gr. each morning, alternated every other day for 6–8 days, are probably the best diuretics we have today.

ERRATUM

Please insert this between pages 18 and 19 of *Present Concepts in Toxemia of Pregnancy*—McCall (October 1959 DM).

Page 18, last paragraph, 4th line: Beginning with ammonium chloride, dosages should be in Grams instead of grains.

Fluids should not be restricted, but the patient should be placed on a strict low-sodium, high-protein diet. The patient should be carefully watched for increased blood pressure and albuminuria, as well as the development of symptoms of headache, epigastric pain and blurring of vision. If symptoms do not worsen, the patient usually can be carried on to good viability of the fetus. Once the syndrome of toxemia has been well established, however, it seldom disappears unless there is fetal demise or delivery. When these patients go into labor, it is well to treat them with magnesium sulfate anticonvulsive therapy as a prophylactic measure against the sudden development of severe pre-eclampsia or of convulsions.

Management of Severe Pre-Eclampsia

It becomes obvious that in lieu of the specific therapy for toxemia, the only logical approach to medical therapy is by correcting pathologic physiology. While the present state of our knowledge does not allow this to be complete, the following fundamental principles should be utilized:

1. Relaxation of vasospasm.
2. Avoidance of anoxia.
3. Treatment of the hyperirritability of the nervous system.
4. Other measures:
   a. Bed rest.
   b. Diuresis.
   c. Prevention of cardiac failure.
   d. Prevention of infection.
   e. Protection of the baby with good obstetric management.

All patients with severe pre-eclampsia should be hospitalized immediately. Complete bed rest, sodium restriction, high protein diet, mild sedation, diuretic drugs and careful frequent evaluation for worsening of the condition are in order. Unless some unusual complication supervenes, the patient should follow this regimen for 48 hours, after which time evaluation as to more specific medical or obstetric management should be made.

Vasodilator Therapy

In the past, the only approach to the treatment of severe toxemia, as well as the hypertension and vasoconstriction associated with it, was heavy sedation. Today, we feel that this is a poor approach. The use of agents which relax the spasm of terminal arterioles, thus lowering peripheral vascular resistance and hypertension, and therefore alleviating many of the complications associated with it, has an important place in modern therapy of the severely toxic patient. Most sedatives will only transiently lower blood pressure by causing peripheral vasodilatation without relaxing the spasm within the vital organs. I have demonstrated that heavy sedation, especially barbiturates given intravenously, not only fail to relax the vasoconstriction of the brain, but also add to the anoxia already caused by the disease. It is most important that the type of vasodilators used do not add to the abnormalities already present. These must relax spasm while lowering blood pressure in such a ratio that the circulation of blood may be maintained at normal levels in the important areas of the body.

I have come to the conclusion after several years of basic research and clinical evaluation that a combination of the two drugs Unitensin (cryptenamine, which is a mixture of two of the purified alkaloids of veratrum viride) and Apresoline (hydralazine) given intravenously produce the best results in patients with hypertensive crises. The combination is used so as to take advantage of the renal effect of hydralazine, which is to increase blood flow and often enhances urinary output as well as other fundamental renal functions, and to utilize the over-all ideal homeostatic effects of veratrum viride on all other organs of the body. By using these two drugs in a blend intravenously, the undesirable side effects of each are almost entirely canceled out. Thus, the renal depressing effect of veratrum is forestalled, and the severe tachycardia, hot flashes and increased cardiac output associated with Apresoline therapy is circumvented. Likewise, the patient is not made rigid from the standpoint of her adaptive reflexes with this blended infusion, as happens with Apresoline alone, or with the ganglionic blocking agents. While reserpine

may be used with advantage by itself or in combination in the less severe case, it is my experience that it does not give as good results in the most severe types of toxemia. Vasodilator therapy of the type described is used in the following groups of patients:

1. Patients in labor who exhibit a sudden rise in blood pressure.
2. All cases of eclampsia with blood pressure of 150 systolic or over.
3. Pre-eclamptics who do not respond to routine conservative therapy.
4. Hypertensives with marked superimposed pre-eclampsia.
5. Postpartum patients who have a sudden marked rise in blood pressure.

It has now been established that vasodilator infusion therapy with Unitensen and Apresoline should be an important part of the over-all therapy of the above groups of patients. It will be seen that the indications listed are those of "hypertensive crisis." This therapy is not to be used in the mild pre-eclamptic, the benign essential hypertensive without superimposed toxemia, nor should it be administered for more than 3 consecutive days except under unusual circumstances. The technic used is as follows:

1. 20 mg. of Apresoline and 5 mg. of Unitensen are placed into 500 cc. of 10 or 20% solution of glucose. This mixture is attached to one limb of a Y tube.
2. Plain glucose solution is attached to the other limb of the Y tube.
3. The intravenous infusion of the vasodilator mixture is started at 20 drops per minute.
4. Blood pressure is taken every 5 minutes for the first 2 hours and every 15 minutes thereafter.
5. The inflow of vasodilator infusion is regulated as necessary after each reading to insure the maintenance of blood pressure at a steady level: 110–140/60–90.
6. If the systolic blood pressure reaches a level below 100 mm. Hg, the vasodilator infusion is discontinued temporarily, and the plain water and glucose mixture substituted until the pressure rises to the desired level.
7. In patients for whom medical induction of labor is desirable, a third bottle containing a dilute Pitocin mixture is added.
8. If blood pressure does not drop in 30–45 minutes, with an infusion rate of 60 or more drops per minute, 1 mg. of Unitensen should be added per 100 cc. of solution present.

By the use of these vasodilating agents, our aims are the following:

1. To afford at least temporary relief from intense vasospasm and the damage it inflicts.
2. To insure the maintenance of normal visceral circulation and function through the activity of Apresoline on the kidney combined with the over-all maintenance of homeostasis in other vital organs of the body with Unitensen.
3. To gain valuable time in which to study and evaluate carefully the seriously toxic patient under less threatening circumstances than otherwise would be possible, while preparations are being made for the more definitive therapy of interruption of the pregnancy.
4. To circumvent the necessity of using large amounts of sedation or conduction anesthesia with their harmful effects.

Once patients are stabilized, they are delivered promptly if they are at term, if they are refractory to therapy or represent superimposed pre-eclampsia on pre-existing hypertension or renal disease. Some of these babies are notoriously small and do not grow appreciably in the ensuing weeks because of impaired placental circulation which ultimately leads to intrauterine fetal demise.

If there are no contraindications to induction of labor, vaginal amniotomy is done and 1,000 cc. of 5% glucose solution containing 10 units of Pitocin is attached to the other limb of the Y tube.

An exception is made in our policy of early delivery if the uncomplicated pre-eclamptic responds well to therapy. In these patients, it is in the best interest of the infant to postpone delivery until the 35th or 36th week. Subsequently, we may maintain our patients on small doses of reserpine and/or Apresoline. This will not circumvent fetal death in some cases, but actually there is a better fetal salvage if the patient is under 32 weeks of gestation when this interim treatment is carried out.

Sedation

Our investigations of sedatives have shown that some agents which are quite frequently used are actually harmful to the patient. This is true of intravenously administered barbiturates,

such as sodium Amytal and sodium Pentothal. They cause decrease in oxygen metabolism of the brain, which is indistinguishable from the metabolic depression caused by the disease itself. In addition, they may also depress respiration, so as to be a further cause of anoxia.

It is important, therefore, when choosing a sedative, that the agent be able to control the hyperreactivity of the nervous system without overdepressing it. We feel that magnesium sulfate is the ideal substance in most instances, and utilize 20 cc. of 50% solution given in the buttocks in divided doses intramuscularly. We may also give morphine sulfate, 16 mg., and sodium phenobarbital, 0.4 Gm., intramuscularly, when we are certain that the patient is not in labor. However, we do prefer magnesium sulfate and, in recent years, have used no other sedative whenever the patient is in labor.

Special Considerations During Labor and Postpartum Period

The onset of labor in the toxemic patient presents several possible complicating factors:

1. The delivery of an impaired and premature baby.
2. An increased possibility of convulsions with associated significant maternal and fetal mortality.
3. An increased incidence of premature separation of the placenta, with its added dangers of hypofibrinogenemia and anuria.

The management is the same whether labor be spontaneous or induced. Vasodilator infusion is started if the systolic blood pressure rises to 160 or more. Magnesium sulfate is used for sedation. As an initial dose, it is entirely safe to give 10 Gm. as a 50% solution. We give 10 cc. of this solution deep into each buttock. This is followed by 5 Gm. in 50% solution every 6 hours or as necessary. We utilize the precautionary criteria recommended by Eastman for repeating this medication. There must be positive knee jerks, respirations of 16 or more and a 24-hour urinary output of more than 600 cc. The antidote for magnesium intoxication is 10% calcium gluconate given intravenously.

Our choice of anesthesia for vaginal delivery is pudendal block,

using either the simplified transvaginal technic or the older transperineal method.

Immediately post partum, the patient should be sedated and kept quiet for at least 48 hours. Morphine sulfate, 16 mg. (gr. ¼) and sodium phenobarbital, 0.3 Gm. (gr. V), are given intramuscularly immediately post partum if the patient has reacted from her anesthesia. This is followed by 0.1 Gm. (gr. 1½) phenobarbital every 6 hours.

All patients who have had pre-eclampsia should have a complete renal and cardiovascular survey 8 weeks post partum.

Pre-eclampsia can deteriorate to eclampsia at any time. Seventy per cent of eclampsia occurs just before or during labor, and the remainder in the immediate postpartum period.

Management of Eclampsia

Eclampsia is an emergency which demands therapy but not overtreatment. The same principles of physiologic treatment apply here as in pre-eclampsia. Heavy sedation is not necessary to control convulsions.

1. Vasodilator therapy is started as soon as possible after admission unless the systolic blood pressure is below 150.
2. Morphine sulfate, 16 mg. is given unless the patient is in labor. Only magnesium sulfate is given if the patient is in labor (see #5).
3. Nasal oxygen is administered continually.
4. A suction apparatus to keep the airway clear is placed at the bedside, with constant nursing care. Tracheotomy is indicated whenever there is a poor airway and obvious anoxia. It is especially efficacious when pulmonary edema is present. When heavy sedation is utilized, this procedure is indicated more frequently. It is rarely necessary when vasodilators are used.
5. Intramuscular magnesium sulfate is given as described above. This will usually be all the sedation the patient will need. However, if the eclamptic requires immediate sedation and is in active labor, 20 cc. of a 10% solution of magnesium sulfate is given intravenously. Since the effect of intravenous magnesium sulfate is transient, the intramuscular dosage schedule is started at the same time.
6. Clinical evaluation at frequent intervals and careful nursing care are of prime importance. Attention to details includes:

a. A quiet room.
b. Indwelling catheter.
c. Constant nursing care to record pulse, respirations, and to protect the patient against injury during convulsions.
d. Frequent evaluation of the depth of coma and examination of the lung bases for rales. Digitalis is to be used as soon as the earliest signs of cardiac decompensation occur.

The physician must not become panicky at the sight of a convulsion and further depress these women with intravenous barbiturates.

Remember that once the convulsions are controlled, the disease has not been cured. The eclampsia has merely reverted to a severe pre-eclampsia. The patient's postpartum care is exactly that of the pre-eclamptic.

OBSTETRIC MANAGEMENT

The obstetric management of the toxemic patient is of great importance. Actually, despite all the advances in our knowledge of this disease, interruption of pregnancy remains as the most definitive approach to this condition. Many factors must be taken into consideration, and it is here that a great deal of clinical experience and judgment must be exercised. The evaluation of the patient for indications for delivery and for the types of delivery may be briefly outlined as follows:

Evaluation of patient:

1. Baby size.
   a. Clinically and by x-ray.
2. State of the cervix.
   a. By vaginal examination.
3. Severity of toxemia.
   a. By eyegrounds.
   b. By blood pressure.
   c. By urinalysis.
   d. By urinary output.
   e. By retention of nitrogen (BUN).
   f. By presence of convulsions and coma.
   g. By other complications.
4. Circulatory Sufficiency of the Placenta.

When toxemia develops early in pregnancy (28–30 weeks), especially in patients with pre-existing hypertensive or renal disease, the fetus may not grow normally because of placental insufficiency on the basis of infarction, fibrosis and atheromatosis. There is the danger that the fetus may die in utero either before or during labor. All such patients should have the height of the uterine fundus measured frequently. If fetal growth, as shown by such measurements, is faulty, a Pitocin Test should be performed.

I have utilized this test, as described by T. L. Montgomery, to good advantage. Just enough Pitocin is given (either intravenously or by intramuscular injection of 0.1–0.3 minims) to produce several uterine contractions. The fetal heart rate is plotted exactly for 20–30 minutes before Pitocin injection and compared with a record taken during and immediately after a uterine contraction. When the placenta is small and badly infarcted, a contraction will so compromise the fetal circulation that fetal heart tones are slowed, frequently disappear for several seconds, and are re-established following contraction only after a transient period of irregularity. This indicates that placental circulatory insufficiency is present to such a degree that normal labor would most probably cause the death of the infant. Cesarean section is performed on these patients if the baby appears to be large enough to survive extrauterine life. If the fetal heart tones are not affected in the way described, vaginal delivery is anticipated.

Indications for delivery:

1. Severe toxemia after the 35th week.
2. Increasingly severe toxemia (at any phase of gestation).
3. Signs of placental insufficiency.
4. Eclampsia.
   a. 24–72 hours after first convulsion.
5. Other complications.
   a. Abruptio placenta.
   b. Fetal distress.
   c. Kidney failure.

Types of delivery:

1. Vaginal.
   a. Stripping membranes and Pitocin drip.
   b. Rupture membranes.

(1) Only if vertex is well fixed in pelvis.

c. Repeated Pitocin drip (unripe cervix).

d. Delivery with:

(1) Pudendal block or local anesthesia.

(2) Magnesium sulfate sedation.

(3) Vasodilators for blood pressure of 160 or over.

2. Abdominal.

a. Emergency for mother or baby.

(1) Signs of placental insufficiency.

(2) Deterioration of mother's condition.

(3) Abruptio placenta.

(a) Fetal indications.

(b) When unable to control mother.

(c) Kidney shutdown.

(4) Obstetric reasons.

b. After failure of medical induction.

c. Delivery with:

(1) Local anesthesia.

(2) Magnesium sulfate sedation.

(3) Vasodilators for blood pressure of 160 or over.

SUMMARY

1. Toxemia of pregnancy continues to be one of the serious complications of human gestation and remains a common cause of maternal and perinatal mortality.

2. Some recent basic concepts of etiology, pathologic anatomy, pathologic physiology and diagnostic methods have been reviewed.

3. Medical management of mild and severe pre-eclampsia and of eclampsia is based on the correction of significant pathologic physiology present.

4. The indications and logic for obstetric management are outlined.

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